ENHANCEMENT OF FIBROBLAST PLASTICITY FOR TREATMENT OF DISC DEGENERATION

[0001] This application claims priority to U.S. Provisional Patent Application Ser. No. 62/666,816, filed May 4, 2018, which is incorporated by reference herein in its entirety.

TECHNICAL FIELD

[0002] Embodiments of the disclosure concern at least cell biology, molecular biology, biochemistry, and medicine.

BACKGROUND

[0003] Generally speaking, the spine can be thought of as a column made of vertebrae and discs. The vertebrae provide the support and structure of the spine while the spinal discs, located between the vertebrae, act as cushions or "shock absorbers." These discs also contribute to the flexibility and motion of the spinal column. As the body ages, the discs often develop deformities such as tears or cracks, or simply lose structural integrity, for example discs may bulge or flatten. These impaired discs can affect the anatomical functions of the vertebrae because of the resultant lack of proper biomechanical support and are often associated with chronic back pain. Disc degeneration may occur as part of the normal aging process or as a result of traumatic injury to the soft and flexible disc positioned between the vertebrae. The resulting structural collapse under load may cause, among other things, significant pain and loss of motion. Because of these conditions, other health issues may result. Several means of treating disc degenerative disease involve administration of regenerative cells into the disc as a source of regenerating atrophied or apoptotic cells in the nucleus pulposus of the disc. Unfortunately, current techniques for generating regenerative cells are limited. The disclosure provides means of generating cells useful for the treatment of disc degenerative disease.

BRIEF SUMMARY

[0004] The present disclosure is directed to methods and compositions related to treatment and prevention of disc diseases in a mammalian individual, including disc degenerative disease. In particular embodiments, methods are disclosed that are directed to preparing fibroblasts for treatment and prevention of degenerative disc(s) in an individual. The fibroblasts are enhanced for such treatment and prevention methods by exposing them to one or more agents and/or one or more conditions such that the exposure enhances one or more capabilities and/or one or more activities of the treated cells.

[0005] In one embodiment, there is a method of preparing fibroblasts for use in treatment of a degenerative disc in an individual, comprising the step of exposing fibroblasts to one or more of the following de-differentiation agents: a) one or more histone deacetylase inhibitors; b) one or more DNA methyltransferase inhibitors; c) umbilical cord blood serum; d) one or more GSK-3 inhibitors; and/or e) one or more components from donor cells. In particular embodiments, the fibroblasts are exposed to reversin, cord blood serum, lithium, a GSK-3 inhibitor, resveratrol, pterostilbene, selenium, (-)-epigallocatechin-3-gallate (EGCG), valproic acid and/or salts of valproic acid, or a combination thereof. In some cases, the one or more components from the donor cells comprises RNA, DNA, protein, and/or cytoplasm from donor cells. When the agent is one or more components from donor cells, the fibroblasts may be cultured with one or more DNA demethylating agents, HDAC inhibitors, and/or histone modifiers. The fibroblasts may be further exposed to one or more proteolysis inhibitors, inhibitors of mRNA degradation, or both. Examples of proteolysis inhibitors include one or more protease inhibitors, proteasome inhibitors and/or lysosome inhibitors. The histone deacetylase inhibitor may be selected from the group consisting of a) valproic acid; b) sodium phenylbutyrate; c) butyrate; d) trichostatin A; and e) a combination thereof. In specific embodiments, the umbilical cord blood serum is used as part of culture media at a concentration of 0.1-20% volume/volume of the tissue culture media. The exposing step may occur in media having an oxygen content from 0.5 to 21%. The exposing step may occur in media having glucose content below 4.6 g/l.

[0006] In certain embodiments, an effective amount of the prepared fibroblasts are administered to an individual in need thereof. An effective amount of the prepared fibroblasts may be administered into the nucleus pulposus and/or the annulus fibrosus of the individual. The fibroblasts may be administered to the individual in or with a carrier, such as one that comprises one or more of beads, microspheres, nanospheres, hydrogels, gels, polymers, ceramics, and collagen platelet gels. The fibroblasts may be administered to the individual with (though not necessarily in the same composition) one or more additional therapeutic agents, such as one or more vitamins; nutritional supplements; hormones; glycoproteins; fibronectin; bone morphogenetic proteins (BMPs); differentiation factors; antibodies; gene therapy reagents; anti-cancer agents; genetically altered cells; and/or pain killers. In some cases, the fibroblasts are administered to the individual with one or more growth factors, although not necessarily in the same composition. In certain embodiments, the administration step may further comprise removal of at least some nucleus pulposus and/or annulus fibrosus of the individual.

[0007] The foregoing has outlined rather broadly the features and technical advantages of the present invention in order that the detailed description of the invention that follows may be better understood. Additional features and advantages of the invention will be described hereinafter which form the subject of the claims of the invention. It should be appreciated by those skilled in the art that the conception and specific embodiment disclosed may be readily utilized as a basis for modifying or designing other structures for carrying out the same purposes of the present invention. It should also be realized by those skilled in the art that such equivalent constructions do not depart from the spirit and scope of the invention as set forth in the appended claims. The novel features which are believed to be characteristic of the invention, both as to its organization and method of operation, together with further objects and advantages will be better understood from the following description when considered in connection with the accompanying figures. It is to be expressly understood, however, that each of the figures is provided for the purpose of illustration and description only and is not intended as a definition of the limits of the present invention.